PCT/EP2004/013339

EP04/13339

INVESTOR IN PEOPLE

The Patent Office
Concept House
Cardiff Road
Newport
South Wales
NP10 8QQ

I, the undersigned, being an officer duly authorised in accordance with Section 74(1) and (4) of the Deregulation & Contracting Out Act 1994, to sign and issue certificates on behalf of the Comptroller-General, hereby certify that annexed hereto is a true copy of the documents as originally filed in connection with the patent application identified therein.

In accordance with the Patents (Companies Re-registration) Rules 1982, if a company named in this certificate and any accompanying documents has re-registered under the Companies Act 1980 with the same name as that with which it was registered immediately before re-registration save for the substitution as, or inclusion as, the last part of the name of the words "public limited company" or their equivalents in Welsh, references to the name of the company in this certificate and any accompanying documents shall be treated as references to the name with which it is so re-registered.

In accordance with the rules, the words "public limited company" may be replaced by p.l.c., plc, P.L.C. or PLC.

Re-registration under the Companies Act does not constitute a new legal entity but merely subjects the company to certain additional company law rules.

PRIORITY DOCUMENT
SUBMITTED OR TRANSMITTED IN COMPLIANCE WITH RULE 17.1(a) OR (b)

Signed

Dated 9 December 2004

nts Form 1/77

Patents Act 1977
(Rule 16)

25NOV03 E854634-2 D02656
P01/7700 0.00-0327306.7

THE PATENT OFFICE
SN
24 NOV 2003
LONDON

Request for grant of a patent

(See the notes on the back of this form. You can also get an explanatory leaflet from the Patent Office to help you fill in this form)

The Patent Office

Cardiff Road
Newport
South Wales
NP10 8QQ

1. Your reference

P15278 (101 003) r2/ro

2. Patent application number
(The Patent Office will fill in this part)

0327306.7

24 NOV 2003

3. Full name, address and postcode of the or of each applicant *(underline all surnames)*

ANGIOMED GmbH & Co.
MEDIZINTECHNIK KG
Wachhausstrasse 6
D-76227 Karlsruhe
Germany

Patents ADP number *(if you know it)*

8620981001

If the applicant is a corporate body, give the country/state of its incorporation

4. Title of the invention

CATHETER DEVICE

5. Name of your agent *(if you have one)*

David Lethem

"Address for service" in the United Kingdom to which all correspondence should be sent *(including the postcode)*

Hoffmann Eitle
European Patent Attorneys
Sardinia House
52 Lincoln's Inn Fields
London WC2A 3LZ

Patents ADP number *(if you know it)*

07156466001

6. If you are declaring priority from one or more earlier patent applications, give the country and the date of filing of the or of each of these earlier applications and *(if you know it)* the or each application number

Country	Priority application number *(if you know it)*	Date of filing *(day / month / year)*

7. If this application is divided or otherwise derived from an earlier UK application, give the number and the filing date of the earlier application

Number of earlier application	Date of filing *(day / month / year)*

8. Is a statement of inventorship and of right to grant of a patent required in support of this request? *(Answer 'Yes' if:*

a) any applicant named in part 3 is not an inventor, or
b) there is an inventor who is not named as an applicant, or
c) any named applicant is a corporate body.
See note (d))

Yes

Patents Form 1/77

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form	0
Description	12
Claim(s)	2
Abstract	-
Drawing(s)	3 + 3SN

10. If you are also filing any of the following, state how many against each item.

Priority documents	
Translations of priority documents	
Statement of inventorship and right to grant of a patent *(Patents Form 7/77)*	
Request for preliminary examination and search *(Patents Form 9/77)*	1
Request for substantive examination *(Patents Form 10/77)*	
Any other documents *(please specify)*	

11. I/We request the grant of a patent on the basis of this application.

Signature

Date 24/11/2003

12. Name and daytime telephone number of person to contact in the United Kingdom

David Lethem
Hoffmann Eitle

020 7404 0116

Warning

After an application for a patent has been filed, the Comptroller of the Patent Office will consider whether publication or communication of the invention should be prohibited or restricted under Section 22 of the Patents Act 1977. You will be informed if it is necessary to prohibit or restrict your invention in this way. Furthermore, if you live in the United Kingdom, Section 23 of the Patents Act 1977 stops you from applying for a patent abroad without first getting written permission from the Patent Office unless an application has been filed at least 6 weeks beforehand in the United Kingdom for a patent for the same invention and either no direction prohibiting publication or communication has been given, or any such direction has been revoked.

Notes

a) If you need help to fill in this form or you have any questions, please contact the Patent Office on 08459 500505.

b) Write your answers in capital letters using black ink or you may type them.

c) If there is not enough space for all the relevant details on any part of this form, please continue on a separate sheet of paper and write "see continuation sheet" in the relevant part(s). Any continuation sheet should be attached to this form.

d) If you have answered 'Yes' Patents Form 7/77 will need to be filed.

e) Once you have filled in the form you must remember to sign and date it.

f) For details of the fee and ways to pay please contact the Patent Office.

CATHETER DEVICE

This invention relates to a catheter device having a shaft, a rapid-exchange guidewire lumen and a distal end which exhibits a sheath which can be withdrawn proximally to release a self-expanding implant such as a stent. To prevent the self-expanding stent moving proximally with the proximally-moving sheath, the catheter device includes a stopper which bears on the stent and resists its proximal movement.

Conventionally, such a catheter device exhibits a shaft comprising an outer tube connected to the sheath and an inner shaft connected to the stopper, whereby the proximal movement of the sheath is accomplished by imposing an endwise tension on the outer tube, with the inner shaft carrying an endwise compression stress, as the stopper at the distal end of the inner shaft works to resist proximal movement of the stent. For examples, see WO 03/003944, WO 03/002020 and EP-A-1095634.

Such conventional systems can work well, and can be of relatively simple construction. However, the present inventor has discovered that they are nevertheless capable of improvement.

One disadvantage noted by the present inventor is that release of the stent requires the medical practitioner to maintain the inner pusher shaft unchanged in axial disposition relative to the site of stenting in the body of the patient, while pulling back on the outer tube of the shaft to release the stent. This pulling back of the outer tube requires relative movement of the outer tube in the bodily lumen (or guide catheter) in which it has been

advanced to the site of stenting. Any friction or resistance to axial movement of the outer tube in the lumen in which it is located hinders the objective of maintaining the stopper in a precise disposition relative to the target stenting site. In practice, it is customary to compensate for axial strain in known systems by positioning the stent slightly distal of the desired end position before commencing stent deployment by pulling back the sleeve. The present invention aims to reduce or eliminate the need for such compensation.

One object of the present invention is to improve positional placement of a self-expanding stent at a target stenting site in a human or animal body, when using a transluminal, catheter-based stent delivery system. According to the present invention, there is provided a catheter device of the type identified above, and which is characterised in that the shaft of the catheter device features a shaft tube with a lumen and with a distal end operatively connected to the stent stopper, the tube lumen being occupied by a pull wire which is arranged to pull back the sheath surrounding the self-expanding stent. The wire can itself be tubular.

It will be appreciated that, with an arrangement in accordance with the present invention, there is no requirement for any axial movement of the outer shaft tube relative to the lumen in which it slides. Instead, since the shaft tube is connected to the stent stopper, it is required that there be no such axial movement. Accordingly, any binding between the shaft tube and any surrounding guide catheter, or bodily tissue of the access lumen, and any friction acting on the outside surface of the shaft tube, is turned by the present invention into an advantage rather than a problem, because it will help to confirm the axial position of the shaft tube relative to the stopper and the stenting site. The more tortuous the access lumen in the body, the more likely it is that there will be no axial movement of the

shaft tube and stopper relative to the intended stenting site.

Furthermore, a shaft tube has more inherent resistance to elastic axial compression than a mere wire within the lumen of the tube. Thus, regardless how great are the tensile stresses imposed on the pull wire during the push-pull activity of stent release, there should be less unwanted proximal movement of the stopper from the intended site of stenting.

Furthermore, the means for pulling back the sheath can also be of metal and also with a high capacity to resist axial strain, increasing the precision with which the operator of the catheter device can control the progressive withdrawal of the sheath and release of the stent. Many doctors prefer to release a self-expanding stent in a step-wise movement. If the pulling system stretches, then a step-wise movement can have the consequence of a time-dependent response at the distal end of the system, and a relaxation of the pulling system between successive pulling steps, with consequent undesirable reverse distal movement of the sheath or else "lost movement" in the pulling system as it once again strains to take up the pull tension with successive step-wise pulls at the proximal end of the system.

Thus, the shaft tube is conveniently a stainless steel hypo tube and the pull wire is conveniently of metal, such as a stainless steel wire, either solid or hollow. Furthermore, while the sheath will very likely be of polymer, it can be made resistant to elastic stretching during proximal withdrawal and release of the stent by embedding within the annular wall thickness of the polymer sheath a fiber reinforcement such as a braided metal mesh. In such an embodiment, there is effectively a continuous strand of elastic strain-resistant metal in the pulling system, all the way from the proximal end of the pull wire to the distal end

of the polymer sheath, again adding to the precision of proximal withdrawal, and minimising any elastic strain within the system during withdrawal.

The pull wire can be connected to the sheath by, for example, first and second metal rings, one inside the other, and sandwiching the sheath so that one of the metal rings is inside the sheath annulus and the other is outside the sheath annulus. The inside metal ring would normally be welded, soldered or brazed to the distal end of the pull wire (adhesives being generally disfavoured in such stent delivery devices) while the outer metal ring can be swaged down onto the sheath to press the sheath onto the inner metal ring.

The present applicant has developed stent delivery systems which feature a catheter system having a heat-formed tapered distal tip which can help to reduce trauma to the body as the catheter system is advanced in a bodily lumen along its guidewire. In the present invention, it is preferred that the sheath has a tapered distal tip, which can be heat-formed, and which desirably tapers down to an end orifice which fits relatively closely around the cylindrical outside surface of the guidewire.

At the proximal end of the sheath, it will also be attractive to taper the diameter down to a relatively snug fit around the outside of the shaft tube (but not so snug as to resist proximal axial sliding of the sheath along the outside of the shaft tube). It is contemplated to create the proximal guidewire exit port in the tapered proximal end of such a formed sheath, as explained below in more detail in relation to the accompanying drawings.

In another embodiment, the proximal end of the sheath can be joined to a metal collar that defines a proximal guidewire exit port lumen and another lumen to slidably receive the outer tube of the catheter shaft. The collar can be given a

domed shape facing proximally, to facilitate atraumatic withdrawal of the catheter system.

One way of connecting the shaft tube to the stopper is by way of a pusher tube which defines a guidewire lumen and carries the stopper at a location near the distal end of the pusher tube, or at its distal end. The proximal end of the pusher tube would be bonded to one side of the distal end of the shaft tube. Conveniently, both the pusher tube and the shaft tube are of metal such as stainless steel, simplifying the task of bonding together side-by-side the proximal end of the pusher tube and the distal end of the shaft tube, as by welding or brazing. Other means of joining these tube sections will be apparent to those readers skilled in the field, who will also appreciate that adhesive compositions are generally disfavoured.

Distal of the stopper, the pusher tube is not required by the invention to carry any axial compressive stress and in any event should be soft and easily bendable so as to keep the catheter tip as floppy as possible . The compression resistant pusher tube could be extended distally beyond the stopper, all the way to the distal end of the sheath, in order to define a guidewire lumen which extends within the pusher tube all the way to the distal end of the system. Indeed, the pusher tube could extend into an atraumatic tip distal of the distal end of the sheath. In this way, the tapered tip of the sheath could be omitted.

Thus, there can be provided distal of the stopper a pusher tube extension, which continues the guidewire lumen from the stopper to the distal end of the system, but which is of less heavy construction, being formed for example of thin wall polymer tube. Another useful purpose of such a guidewire lumen distal of the stopper is for carrying a radiopaque marker band to indicate the distal end of the stent within the delivery system, so that the radiologist can determine

with precision where the stent in the delivery system is located relative to the target stenting site.

For the sake of completeness, and to put the present invention in the context of the prior art documents seen with hindsight to be helpful in appreciating how the present invention contributes to the state of the art, reference will now be made to EP-A-611 556 and WO 96/39998.

EP-A-611 556 discloses a rapid exchange balloon catheter stent delivery system in which a sheath is pulled back proximally by a pull wire, to expose a stent mounted on a balloon, so that the stent can then be deployed by inflation of the balloon. The stent is not a self-expanding stent, so is not pressing on the luminal surface of the sheath during advance of the delivery system to bring the stent into the location of stenting. Accordingly, the balloon-expandable stent is not liable to be carried proximally by the sheath when the sheath is pulled proximally. Accordingly, there is no need for a stopper to resist unwanted proximal movement of the stent. Accordingly, there is no significant resistance to proximal movement of the sheath. Accordingly, there is no need for the shaft of the system, defining the lumen in which the pull wire is located, to be resistant to axial compressive stresses. The problem of designing a system to deliver a self-expanding stent which maintains the axial position of the stent correct during stepwise release of the stent is not a problem experienced with balloon-expandable stent delivery systems.

Conversely, WO 96/39998 is a disclosure which is concerned with systems which will resist endwise compression during delivery of a self-expanding stent and proximal withdrawal of a sheath surrounding such a stent. The problem is addressed by providing within the delivery system an inner core which is resistant to endwise compression, and providing a stopper near the distal end of the inner core. Thus, the pull wire is

not housed within the lumen of the element that is in endwise compression during stent release but instead, is lying side-by-side with the element that is subject to endwise compression. Any capability that the outer sheath of the system might have to carry endwise compression stress remains unutilised.

For a better understanding of the present invention, and to show more clearly how the same may be carried into effect, reference will now be made, by way of example, to the accompanying drawings, in which:

Fig. 1 is a longitudinal diametrical section through the distal end zone of a catheter device in accordance with the invention;

Fig. 1A is the identical section, at larger scale, through the distal part of the distal zone of Fig. 1;

Fig. 1B is an identical section, at larger scale, through the proximal part of the distal zone of Fig. 1; and

Fig. 2 is a longitudinal diametrical section, at enlarged scale, of the junction between the pusher tube and pusher tube extension of the embodiment of Fig. 1.

Referring to Figs. 1, 1A and 1B, a self-expanding stent 10, or stent graft, lies inside the distal end zone 12 of a sheath 14 with a tapered distal tip 16 and a heat-formed proximal end 18 which defines the orifice 20 of a proximal guidewire exit port for a guidewire 22. Being a self-expander, the stent 10 is, at least at body temperature, putting compressive stress on the luminal surface of the sleeve 14 in the distal end zone 12. Proximal of the stent 10, and on the abluminal surface 24 of the sleeve 14, is a swaged marker band 26 of radiopaque metallic material, which is pressing radially inwardly the material of the sheath 14

within the band 26. Radially inside the sheath at this point is a metal annulus 28 which is itself put under radially inwardly compressive stress by the material 30 of the sheath 14 inside the marker band 26. Thus, the sheath material 30 is compressed between metal bands inside (28) and outside (26) the sheath 14. Brazed to the annulus 28 is a pull wire 32 which runs from the annulus 28 all the way back to the proximal end of the catheter device, whereby endwise tensile stress imposed on the proximal end of the pull wire 32 will pull proximally the annulus 28 and thereby impose on portions of the sheath 14 distal of the annulus 28 an endwise tensile stress, for pulling the sheath 14 proximally with respect to the stent, to release the stent. At the same time, portions of the sheath 14 proximal of the annulus 28 will be pushed proximally.

A pusher annulus 40 is located in the lumen of the sheath 14 just proximal of the stent 10. Its purpose is to resist proximal movement of the stent 10, when the sheath 14 is withdrawn proximally from the stent 10. It can also serve as a radiopaque marker band to indicate the proximal end of the stent 10. The pusher annulus 40 is brazed or welded or otherwise fixed to a pusher tube 42 which is conveniently of stainless steel (PHYNOX™) and which has its distal end 44 distal of the pusher annulus 40 and within the lumen of the stent 10. The proximal end 46 of the pusher tube 42 is arranged side-by-side with the distal end 50 of a shaft tube 52 of the catheter device which extends all the way to the proximal end of the catheter device and is conveniently provided as a stainless steel hypo tube. The lumen of this shaft tube 52 carries the pull wire 32. The overlapping portions 46 and 50 of the pusher tube and shaft tube are bonded to each other, conveniently by brazing, so that they effectively form a single metal strand from the proximal end of the catheter device to the stent pusher annulus 40. As can be seen in Fig. 1 and Fig. 1B, the end orifice 54 of the pusher tube 42 is co-linear with the orifice 56 in the heat-

formed end 18 of the sheath 14, which defines the proximal guidewire exit lumen. Thus, when a guidewire 22 is advanced through the guidewire lumen of the catheter device by introducing it into the end orifice 58 of the tapered distal tip 16 of the sheath 14, the end of the guidewire will advance proximally along the pusher tube and exit through the port 56.

With reference to Fig. 1A and Fig. 2, we will now explain the structure of the pusher tube extension, distal of the pusher annulus 40, and located between that annulus and the end orifice 58 at the distal end of the sheath 14.

The metal pusher tube 42 extends for a short distance distally of the pusher annulus 40. A distal extension inner catheter 68 of polyimide abuts the distal end of the pusher tube 42 and is secured to that pusher tube by a shrink tube 70 radially overlying the distal end of the pusher tube 42 and the proximal end of the inner catheter 68. This shrink tube 70 is of PET (which shrinks radially downward to grip both these abutting portions).

Fig. 2 shows the distal end 72 of the distal extension inner catheter tube 68 and a bore 69 within it, open to the distal end of the inner catheter 68, and terminating proximally at an end-to-end butt joint with the distal end of the metal pusher tube 42. A tip extension catheter 60 of PEBAX polymer receives the distal end 71 of the inner catheter 68, so that its proximal end 67 overlaps the abluminal wall of the catheter 68. Around the distal end zone 72 of the catheter 68, and sandwiched between the distal catheter 68 and the proximal end zone of the tip catheter 60, is a second radiopaque metal marker band 74, and the whole assembly is bonded together with a cyanoacrylate adhesive composition. The PEBAX tip extension catheter 60 extends into the tapered lumen of the taper 16 of the distal end of the sheath 14.

Of note is that the bore 75 of the catheter 60 is contiguous and smooth with the bore 69 of the catheter 68 for smooth progress of a guidewire. Catheter 60 is soft and floppy but has a larger outside diameter than catheter 68, which helps to ease the end orifice of the sheath 14 open when it begins to withdraw. Proximal end 67 of catheter 60 is tapered inwardly. This is because, should a physician decide to sheath the distal end of the delivery system after stent deployment by re-advancing the sheath distally, the tapered tip 16 of the sheath is required to advance distally back onto the abluminal surface of catheter 60 and the taper 67 helps that advance.

Reverting to Fig. 1A, fixed to the lumen surface of the sheath 14, just proximal of the tapered tip zone 16, is a third radiopaque metal marker band 76 and it will be seen that this marker band lies radially outside the second marker band 74 within the distal extension inner catheter 68.

In use, the distal end zone of the catheter system, as shown in the drawings, is advanced along a bodily lumen to a stenting site. When all is ready for deployment of the stent 10, an endwise tension is applied to the pull wire 32, while the proximal end of the shaft tube 52 is restrained from endwise movement, reactive or otherwise. Endwise translation of the pull wire 32 results in proximal movement of the sheath 14. Holding the endwise position of the shaft tube 52 holds the endwise position of the pusher annulus 40 which in turn prevents any proximal movement of the stent 10 with the proximally withdrawing sheath 14.

Progressively, the sheath 14 withdraws proximally relative to the stent 10, having the effect of stretching the distal tip 16 of the sheath 14 over the radially outward surface of the stent 10, leading to progressive release and radial expansion of the stent 10, from its distal end toward its proximal end.

Note that, before there is any relative movement of the sheath 14 and pusher annulus 40, the radiologist "sees" only two marker bands, namely the first marker 40 and the radially superimposed second and third marker bands 74 and 76. However, once the sheath 14 starts to withdraw proximally, the radiologist can see the third marker, at a position proximal of the second marker. Clearly, when the third marker has moved proximally to approach, pass over, and then move proximally away from the first marker 40, one has confirmation that the stent 10 has been deployed, by full proximal withdrawal of the sheath 14.

During proximal withdrawal of the sheath 14, it will be appreciated that the proximal end 18 of the sheath 14 slides proximally over the outside surface of the shaft tube 52.

It will appreciated that there should be no endwise movement of the shaft 52 relative to its surrounding entities, whether a bodily lumen or the lumen of a guidecatheter, during deployment of the stent 10. This is an opportunity for enhancement of precision of the placement of the stent, because any friction between the outside surfaces of the shaft tube 52 and the surrounding structures will only tend to confirm the location of the pusher annulus with respect to the body of the patient, and thereby the location of the stent 10 with respect to the body of the patient.

Further, the friction forces between the pull wire 32 and the luminal surfaces of the shaft tube 52 ought to be very small or minimal, as should any frictional forces between the withdrawing sheath 14 and the outside surface of the shaft tube 52, at the proximal end 18 of the sheath. Further, as the sheath 14 is relatively short in proportion to the catheter device as a whole, any friction between the outside surfaces of the sheath 14 and the surrounding bodily tissue ought also to be usefully smaller than in conventional systems where the full length of the stent deployment

catheter must be moved relative to its surroundings. All of this elimination of unwanted and unhelpful friction is advantageous to the person deploying the stent, because any tactile feedback should relate more closely to events at the stent itself, and any force input at the proximal end of the device should be more completely delivered to the components around the stent 10 at the distal end of the device. There should be less lost motion in the system between the proximal and distal ends, less hysteresis, and less discrepancy between the amount of force applied at the proximal end and the amount of force delivered to the components surrounding the stent. It should be possible, with the system proposed herein, to enhance the position of stent placement, and the degree of confidence that users have when deploying stents, that the stent has been deployed smoothly and correctly.

As to design variations, the following will be evident to those skilled in the art, but so too will many more design possibilities, within the relevant published state of the art but not mentioned here.

The sheath need not include braiding. The pull wire can be threaded directly to the braiding, thereby avoiding the need for any pulling annulus between the pull wire and the sheath. Neither the distal end nor the proximal end o the sheath need be tapered. An atraumatic tip to the device can be carried on the pusher sub-system that includes the stent stopper.

Implants to be delivered by the device need not be stents and stent graft. For example, filters can be deployed with the device.

Those skilled in the art will appreciate how to build an actuator for the proximal end of the device. A suitable basis is the deice described in WO 02/087470, modified to accommodate the radial inversion of the push/pull elements.

Claims

1. A catheter device having a shaft, a rapid-exchange guidewire lumen and a distal end which exhibits

a sheath which can be withdrawn proximally to release a self-expanding implant and

a stopper to prevent proximal movement of the implant when the sheath moves proximally

characterised in that the shaft exhibits

a pull wire for pulling back the sheath

a shaft tube with a lumen containing the pull wire and with a distal end operatively connected to the stopper.

2. Catheter device as claimed in claim 1, wherein the shaft tube is a stainless steel hypo tube.

3. Catheter device as claimed in claim 1 or 2, wherein the pull wire is of metal.

4. Catheter device as claimed in any one of the preceding claims, wherein the sheath is of polymer with fiber reinforcement within the polymer wall thickness.

5. Catheter device as claimed in claim 4, wherein said reinforcement fibers are braided metal strands.

6. Catheter device as claimed in any one of the preceding claims, wherein the pull wire is connected to the sheath by first and second coaxial metal rings, one radially inside the sheath and the other radially outside the sheath.

7. Catheter device as claimed in claim 6, wherein the metal ring outside the sheath is swaged down onto the sheath.

8. Catheter device as claimed in any one of the preceding claims, wherein the sheath has an inwardly tapered distal tip.

9. Catheter device as claimed in any one of the preceding claims, wherein the polymer sheath has a formed proximal end which fits snugly around the outside of the shaft tube and defines a proximal guidewire exit port.

10. Catheter device as claimed in any one of claims 1 t 8, and including a collar having a peripheral surface and first and second lumens, wherein

i) the shaft tube is slidably received in the first lumen

ii) the second lumen defines a proximal guidewire exit port lumen; and

iii) the peripheral surface carries the proximal end of the sheath

with the collar sliding proximally along the shaft tube during proximal withdrawal of the sheath.

11. Catheter device as claimed in any one of the preceding claims and including a pusher tube which defines a guidewire lumen and carries said stopper, and is bonded at its proximal end to one side of the distal end of the shaft tube.

12. Catheter device as claimed in claim 11, further including a pusher tube extension which continues the lumen of the pusher tube, distal of the stopper, distally to the region of the distal tip of the sheath.

13. Catheter device as claimed in claim 12, wherein the pusher tube extension carries a distal radiopaque marker band.

Fig. 1

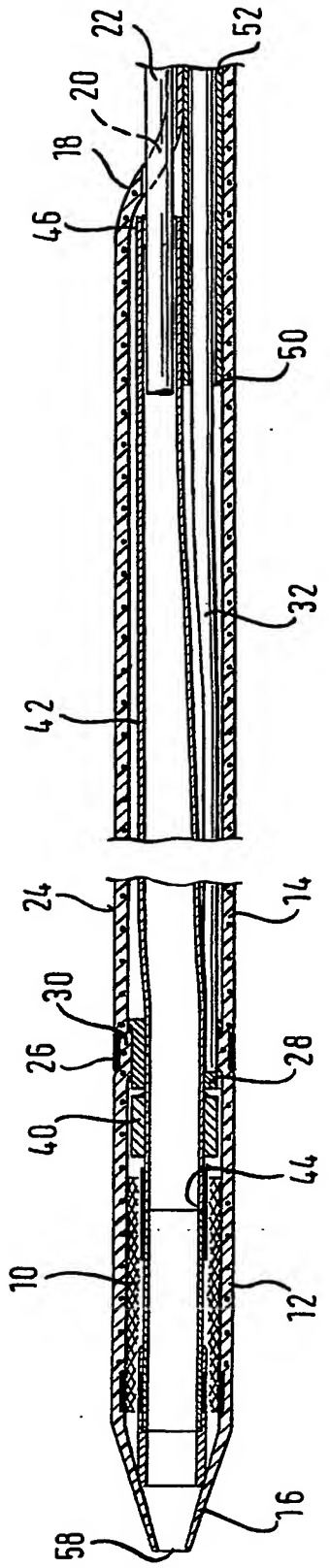
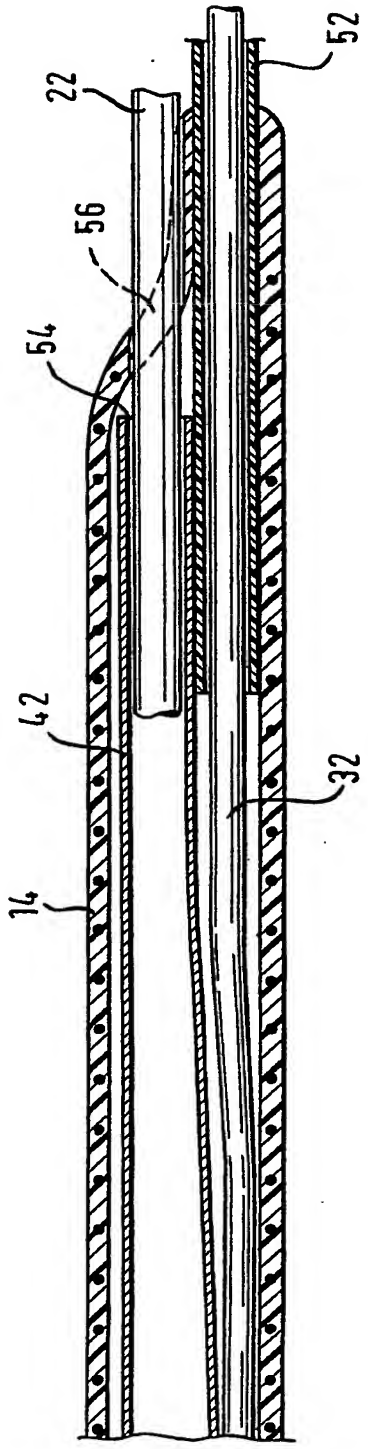

22
52
20
18
46
50
32
42
24
14
30
26
28
40
44
10
12
16
58

Fig. 1B


52
22
56
54
42
32
14

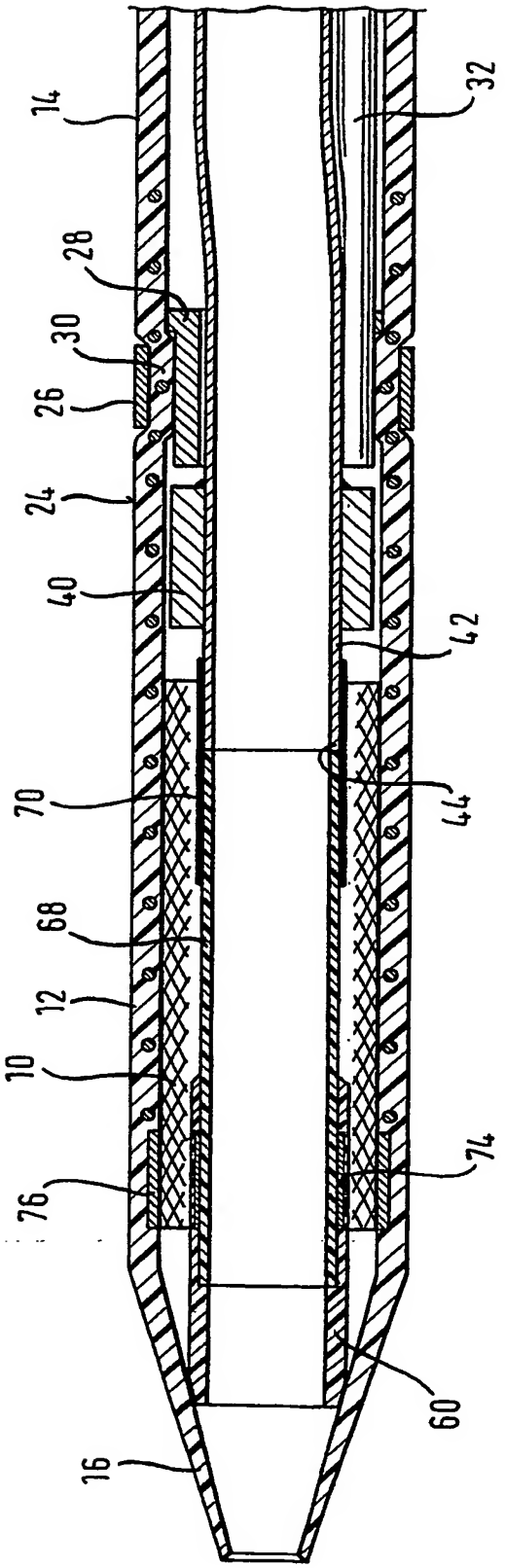


Fig. 1A

Fig. 2